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(54) Title: CERAMIC PROCESSING AND PRODUCTS (57) Abstract A novel method of processing sinterable powders into sintered ceramic products of calcium phosphate compounds, such as hydroxylapatite, involving agglomeration of fine particles with a binding agent and extraction of the binding agent from the agglomerates prior to sintering. The sintered agglomerates have a porosity, particle size and spherical shape which provides a unique combination of advantageous properties when employed as implant materials.		

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CERAMIC PROCESSING AND PRODUCTS

Field of the Invention

The invention disclosed in this application relates to a novel method of processing sinterable powders into sintered ceramic products involving agglomeration of fine particles with a binding agent and extraction of the binding agent from the agglomerates prior to sintering. This application also relates to novel forms of aluminum oxide, hydroxylapatite, and tricalcium phosphate ceramic products prepared in accordance with the method of this invention, as well as novel intermediate products useful to prepare the novel ceramic products of this invention.

Background of the Invention

Bone prostheses are often needed for temporary or permanent use in man or animals. A wide variety of different biocompatible materials have been developed for use as bone prostheses, including, for example, natural or synthetic mineral materials, metals, such as Vitallium™, stainless steel and chromium alloys, as well as organic resins, such as silicone rubbers. The foregoing materials may be employed, for example to: (1) replace a portion of bone which has been lost due to accident or disease, or (2) reinforce a portion of bone which has atrophied or suffered a reduction in mineral content.

In some individuals the alveolar ridge becomes abnormally thin and unable to support either natural or artificial teeth. The support or rebuilding of the alveolar ridge has, therefore, become an important step in the treatment of those individuals suffering from a

weakening in the alveolar ridge due to periodontal disease or other causes. Mineral materials of both synthetic and natural origins have been employed for bone restorative purposes in the alveolar ridge and, hence, to prevent tooth loss due to bone loss in the alveolar ridge.

Many of the same synthetic and naturally occurring biocompatible materials which have been employed for bone prostheses have also been employed for dental restorative purposes. In particular, calcium phosphates, such as hydroxylapatite, tricalcium phosphate (whitlockite) and mixtures thereof have been widely reported in the literature as suitable for use as bone prosthesis as well as for dental restorative purposes. See, e.g. Monroe, et al., J.Dent.Res. 53, p. 1353 et seq. (1974); Bett et al., J.A.C.S. 89, p.5335 et seq. (1967); Kutty, Indian J.Chem. 11, 695 (1973).

Hydroxylapatite is a naturally occurring mineral present in phosphate rock.

Hydroxylapatite also constitutes the mineral portion of natural bone and tooth. As such it is highly biocompatible and has a thermal coefficient of expansion quite similar to tooth enamel.

As discussed in greater detail below, in accordance with the preferred embodiments of the method of this invention, fine dry particles of a hydroxylapatite powder are agglomerated with a binding agent into sinterable spheroidal agglomerates. The binding agent is removed from the spheroidal agglomerates and then they are sintered to provide spheroidal ceramic particles

of hydroxylapatite having a uniform network of micropores extending throughout the ceramic product.

U.S. Patent No. 4,097,935 (hereinafter '935) sets forth a description of a method for preparing a maximally densified, pore-free hydroxylapatite ceramic body. In accordance with the '935 patent the dense, pore-free ceramic body described therein may be prepared by sintering (under specified conditions) a shaped body or mass prepared from an aqueous gelatinous precipitate of hydroxylapatite. The '935 patent teaches away from the use of both products and processes which employ fine particles of hydroxylapatite as starting materials in the preparation of the dense, pore-free ceramic products described in the '935 patent. In this regard the '935 patent states:

"It is critical, in the above process, to prepare the hydroxylapatite as a gelatinous precipitate from aqueous solution for it is only in this cohesive gelatinous state that hydroxylapatite can be shaped or molded and then dried and sintered to produce a ceramic body. Dry particulate or granular hydroxylapatite cannot be reconstituted into the cohesive gelatinous state...Moreover although powdered hydroxylapatite can be compressed into a shaped body, such as a tablet, when sintered according to the method of this invention the product obtained is highly porous and does not fracture along smooth planes but simply shatters." (Col. 9, lns. 22-39).

In contrast to the foregoing, the method of this invention employs dry particulate

hydroxylapatite as the starting material in a novel method employed to prepare porous hydroxylapatite ceramic particles having a network of micropores extending throughout the ceramic product.

The '935 patent also discloses means for introducing pores into the ceramic bodies produced in accordance with the method described in that patent. In this regard the '935 patent states that pores may be introduced by drilling or machining holes in the non-porous ceramic product, or by mixing an organic binder with a body of the gelatinous hydroxylapatite precipitate prior to sintering. The binder is said to volatilize during sintering to produce pores in the ceramic product. The sintered body would then have to be ground, or comminuted in some other way to provide a particulate ceramic product.

Unlike the method described in the '935 patent, in accordance with applicant's method, a binding agent is not added to a gelatinous precipitate of hydroxylapatite, and in producing applicant's final ceramic it is not a sinterable body prepared by adding a binding agent to an aqueous gel which is ultimately sintered. Rather, contrary to the method described in the '935 patent, in accordance with applicant's method the binding agent is employed to agglomerate together fine dry particles of hydroxylapatite, and it is applicant's novel agglomerate of dry hydroxylapatite particles which is sintered in accordance with the method of the present application.

hydroxylapatite particles which is sintered in accordance with the method of the present application.

Biocompatible compositions suitable for use as a dental filling material have been prepared by mixing finely divided ceramics such as sintered hydroxylapatite with a hardenable binder material. In addition, moist ceramic particles of hydroxylapatite have been employed as a biocompatible packing material to fill the voids or lesions caused by advanced periodontal diseases. The ceramic particles used have typically been employed in the form of very finely divided ceramic powders made up of particles in the range of about 10 to about 60 mesh.

Fine particles of calcium phosphate ceramics suitable for use in such filling or packing compositions may be prepared by grinding larger particles or masses of the ceramic down to fine particles within the desired particle size range. The grinding step may be conducted before or after sintering. However, in order to obtain a ceramic powder made up of particles within a desired size range, particles larger and particles smaller than desired must be separated by sieving or by another particle classification process, from the mass of particles produced by the grinding step. Thus, grinding processes typically yield a fraction of ceramic particles which are smaller than the desired particle size range, and which are, often simply discarded as waste. Moreover, the ceramic particles produced by grinding are typically not uniform in shape, and

possess sharp edges or "points" which could lead to local inflammation when placed in contact with tissue. It will be appreciated by those skilled in the art that the term "mesh" as used herein refers to particle size as determined on standard sieves and that while there is some variation in the screen size used with different standards those variations are so small, e.g., See, Kirk-Othmer Encyclopedia of Chemical Technology 18:318-319, 2d ed. (1969), that they are insignificant for purposes of this invention. Accordingly, the mesh sizes may be measured in accordance with e.g., U.S. Bureau of Standards, British Standard, Tyler Standard, or the like.

Ground hydroxylapatite particles and other ceramic particles having sharp edges or points can be mechanically treated to render the particles substantially spheroidal in shape and smooth. However, such mechanical procedures involve extensive milling to remove the sharp edges from the ceramic particles. The process itself is very cumbersome, and the yields quite low.

Conventional molding, casting or pressing operations, which do not involve grinding or milling, are generally suitable for the preparation of smooth round ceramic particles. However, in the case of calcium phosphate and other ceramics intended for use in bone or tooth restorative compositions, particles on the order of 20-40 mesh are often desired, and such particles are too small to be produced by such conventional fabrication processes known to be

useful to prepare round smooth particles.

It is an objective of this invention to provide a substantially waste-free, high-yield, ceramic particle-forming process which may be employed to prepare ceramic particles which are substantially spheroidal in shape, and are within a desired particle size range.

It is a particular objective of this invention to provide a high-yield process for the preparation of biocompatible ceramic particles, especially particles of calcium phosphate and aluminum oxide ceramic which are substantially spheroidal in shape and within about the 10 to about 80 mesh range. The spheroidal ceramic particles produced by the process of this invention are free of sharp edges or ridges capable of producing local irritation when placed in contact with tissue. As such, the spheroidal ceramic particles of this invention are suitable for use as the ceramic component of hardenable binder compositions formulated for use for dental or bone restorative processes.

Brief Description of the Invention

In accordance with the foregoing, this invention provides a high-yield method for preparing sintered ceramic particles which comprises the steps of binding together fine particles of a sinterable inorganic powder to provide sinterable particulate agglomerates within a desired size range. The fine particles of the sinterable powder are bound together to form the agglomerate with a binding agent, such as polyvinyl alcohol, hydroxypropyl cellulose,

polyvinyl pyrrolidone, starch, pregelatinized starch or the like. The binding agent is removed by an extraction step and the agglomerate may then be sintered to provide the final particulate ceramic product.

In the preferred embodiments of the method of this invention, fine particles of sinterable hydroxylapatite and/or whitlockite are agglomerated together with a binding agent to provide sinterable agglomerates which are spheroidal in shape. The agglomerate is subjected to liquid extraction or elevated temperatures in order to substantially eliminate the binder from the agglomerate prior to subjecting the agglomerate to higher temperatures in order to complete the sintering process.

It has been found that when the calcium phosphate (e.g. hydroxylapatite and/or tricalcium phosphate) based agglomerate of this invention is sintered at elevated temperatures, the individual inorganic particles which comprise the agglomerate meld together to provide strong, free-flowing, structurally stable ceramic particles. In addition, the finally sintered agglomerate will include a network of micropores extending throughout the particles. Advantageously, the microporous structure of the particle provides sites for tissue ingrowth and attachment, while the smooth surface of the particles prevents the inflammatory response noted in connection with the rough and irregular surfaces of untreated ground ceramics.

In addition to the advantages mentioned

above, the ceramic particle-forming process of the invention may be conducted such that only a minor amount of the finely powdered ceramic starting material is wasted. In accordance with the process of this invention, agglomerates which are smaller than desired, or any starting ceramic powder which is not agglomerated, may be reused in a subsequent agglomerating process. Similarly, agglomerates which are larger than desired may simply be re-ground and used in a subsequent agglomerating process.

Detailed Description of the Invention

In accordance with the first step of the process of this invention, sinterable agglomerates are prepared by adhering together fine particles of sinterable powder with a binding agent. The binding agent may be any material which effects adhesion between the particles to be agglomerated, and can be eliminated from the agglomerates without leaving a residue that interferes with the sintering or biological properties of the finished product. Suitable binders include organic polymers, preferably polyvinyl alcohol, polylactic acid, hydroxypropyl cellulose, starch, pregelatinized starch and polyvinyl pyrrolidone.

The initial particle size of the fine sinterable powder starting material employed to form the agglomerate is preferably in the range of about 1 to about 75 microns, and most preferably in the range of about 5 to about 50 microns. The fine sinterable powder may be prepared by conventional methods, such as by grinding or milling larger particles or masses of a sinterable

material. However, as described in greater detail below, it is preferred to prepare the finely divided ceramic powder by a spray-drying process. Spray-drying is preferred because it provides a better than 90% yield, provides particles within a narrow particle size range, and provides an easy-to-handle, free-flowing powder.

The sinterable agglomerate may be prepared by applying the binding agent (or a solution of the binder) to a fluidized bed of the ceramic powder. For example, dry and finely ground hydroxylapatite powder may be charged into a Glatt Powder Coater, Model No. GPCG 5-9 (manufactured by Glatt-Air Techniques, Inc. of Ramsey, New Jersey) which fluidizes and agitates the powder particles, while the binder is fed at a controlled rate onto the fluidized bed of particles. In the Glatt Powder Coater the fine powder is fluidized by the introduction of a stream or jet of air into the device which "puffs up" the powder particles and suspends them in air. At the same time the powder is agitated in a rotary fashion in the Powder Coater. When the binding agent is sprayed onto the rotating, fluidized bed, the powder particles agglomerate into larger and larger sized agglomerates in a snow-ball-like fashion, as the amount of binder added to the bed increases. The resultant agglomerates are substantially spheroidal in shape.

As an alternative to spraying the binder onto the fluidized bed of fine sinterable particles, the binder may be added as a solid

dispersed within the fluidized bed of fine sinterable particles. In this embodiment of the process, the fluidized bed of the initially added sinterable particles and binder may be sprayed with a suitable liquid, for example, water or an aqueous or other solution of the binder.

For example, following the techniques discussed above, hydroxylapatite powder, having a particle size in the range of about 1 to about 75 microns, may be agglomerated with an organic binder until agglomerates in about the 10 to about 80, preferably about 20 to about 70 mesh range, are formed. The sintered ceramic is typically somewhat smaller in size than the agglomerate from which it is prepared. Thus, it is preferred to sintered agglomerates within a particle size range wherein the largest agglomerates are about 15 - 75% larger, preferably about 30% larger, than the largest ceramic particle desired; while the smallest agglomerates are also about 15 - 75% larger, preferably about 30% larger, than the smallest ceramic particles desired. Thus, prior to sintering, it is preferred to classify the group of particles which are produced by the agglomeration step in order to select agglomerated particles within the appropriate particle size range. The classification of particles may be conducted by sieving, or by any other conventional sorting or particle classification technique.

One of the advantages of the process of this invention is that off-sized agglomerates or any non-agglomerated starting material may be recycled. That is, agglomerated particles which

are smaller than desired can simply be reused in a later batch, while agglomerates that are too large may be ground to a smaller size, and reused during a subsequent agglomeration process. Thus, there should be little or no waste resulting from the agglomeration process. Moreover, as shown by the following Examples, the sintering process may yield 90% or more of sintered ceramic particles within the desired particle size range.

In further embodiments of the method of this invention, the agglomerated particles produced in the manner described above may be employed as core or seed particles in a second agglomeration process. During the second agglomeration process, the previously prepared core particles, which is itself an agglomerate, may be coated with additional layers of binder plus additional fine ceramic particles. Through this embodiment of the method of this invention, one can prepare a sinterable agglomerate made up of a core of one ceramic material, over which a plurality of spheroidal shells or layers of the same or a different ceramic material are formed. Through this embodiment one may also prepare a sinterable agglomerate of hydroxylapatite made up of a core of a given density over which one or a plurality of shells or layers may be formed having a different density than the core agglomerate. A shell or layer may also be applied to the core particle which is made up of an hydroxylapatite having a particle size which is different from the hydroxylapatite particles which make up the core of the sinterable agglomerate.

The sinterable agglomerates of this invention preferably are comprised of about 5% to about 25% by weight of the binder, preferably about 10% to about 15% of the binder, while the agglomerate preferably comprises about 75% to about 90%, and preferably about 85% to about 95% by weight of sinterable ceramic particles of hydroxylapatite, and/or whitlockite or aluminum oxide. Moreover, the bulk density of the agglomerate is preferably about 0.8 to about 1.5 grams/cc, for agglomerates within about the 10 to about 80 mesh range, while for the preferred agglomerates of hydroxylapatite, the bulk density is about 1 to about 1.2 grams/cc for agglomerates in about the 15 to about 30 mesh range.

It should be noted that the sinterable powder employed to form the agglomerate may be in the form of irregularly shaped particles which possess microscopic ridges or points. When these very fine particles are agglomerated into the larger agglomerates (typically in about 10-80 mesh range) and then sintered, the larger sintered ceramic particle possesses a macroscopically smooth surface. In contrast, ceramic particles in the 10-80 mesh range prepared, for example, by grinding larger ceramic particles possess larger surface points or ridges. It is the larger ridges or points of the ground ceramic materials which present a danger of local irritation when such ceramics are placed in contact with tissue.

The agglomerates of this invention are sintered to provide the finished particulate ceramic product. The temperature and duration

employed to sintered the agglomerate may be the same as those one would conventionally employ to sinter the sinterable powder from which the agglomerate was prepared. However, the binder may advantageously be substantially eliminated before the agglomerate reaches the more elevated sintering temperatures by liquid extraction or heating of the agglomerate to a first temperature that is less than the sintering temperature. Preferably, about 75 to 90 wt. percent or more of the binder is removed from the agglomerate particles by the extraction step prior to sintering. If an agglomerate from which excess binder has not been extracted were rapidly heated to sintering temperatures, there is a danger that any excess binding agent present could affect the color of the finished product, e.g., carbonize and produce a dark off-color in the ceramic product.

In one embodiment of the method of this invention, the hydroxylapatite-containing agglomerate is subjected to a preliminary heat treatment, i.e., heat extraction of the binding agent, at a temperature sufficient to eliminate a substantial portion of the binder from the agglomerate leaving at least a sufficient amount of binder so as not to adversely affect the adhering of the particles present in the agglomerate and to provide an agglomerate which may sintered without objectionable coloration by carbonization. This preliminary heat extraction is preferably conducted at temperatures below about 700°C, and more preferably about 500°C or less. Heating is preferably effectuated in an

oven at the rate of about 20°C per minute up to the final temperatures set forth above. Results may be improved by enriching the oven air or other atmosphere with oxygen. However, the actual temperature, heating rate and oven atmosphere employed will be a function of the particular binder selected, air flow in the oven, etc. It has been found that the foregoing heat extraction serves to substantially eliminate the binder while nevertheless providing a structurally-stable agglomerate of hydroxylapatite. The extracted agglomerate of hydroxylapatite particles may then be subjected to elevated sintering temperatures without fear of discolorization due to carbonization of the binder or other adverse effects on the product. The resultant ceramic particle is preferably white, not translucent and biocompatible.

Alternatively, or in addition to heat extraction the binding agent may be removed from the agglomerates with a liquid extraction technique. Liquid extraction involves washing the agglomerates in a liquid preferably a solvent for the binding agent, e.g., isopropyl alcohol, methylene dichloride, methanol and aqueous solutions thereof. Such aqueous solutions may contain about 99 to 80% by wt. organic solvent. The presently preferred solvent is 100% isopropyl alcohol. The particular solvent used and extraction conditions employed will depend on the particular binding agent and agglomerate to be treated and enough binding agent should remain in the agglomerate after extraction to prevent

disintegration of the agglomerate prior to sintering. To effect liquid extraction the agglomerates may be submerged in the liquid for a sufficient period of time, e.g., about 2 or more hours, to substantially eliminate the binding agent from the agglomerate. Heating or boiling the liquid containing submerged agglomerate may accelerate the extraction process and/or enhance the effectiveness of the extraction. A typical liquid extraction involves charging about 1 liter of isopropyl alcohol into an extraction chamber of a Soxhelt-type extractor. Then about 1.5 kg of agglomerated hydroxylapatite including a polyvinyl pyrrolidone binder prepared as described above is mixed with the aqueous isopropyl alcohol and the mixture is heated to reflux for about 72 hours. Thereafter, the liquid containing extracted binding agent (polyvinyl alcohol) is separated from the agglomerate and the agglomerate is dried to constant weight at about 80-110°C.

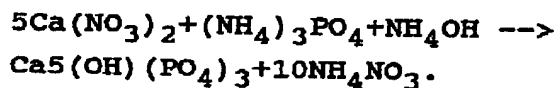
Regardless of the extraction technique employed sufficient binder is preferably removed from the agglomerate to prevent adverse effects on subsequent sintering and/or the physical properties performance and biocompatibility of the finished product. However, if desired an amount of binder may be maintained in the agglomerate to facilitate further processing without undesirable disintegration of the agglomerate particles.

For the preferred agglomerate of hydroxylapatite powder sintering is conducted at a temperature of about 1000°C to 1300°C for about 1

to about 3 hours, most preferably at about 1075°C to 1250°C for about 1 to about 3 hours.

Fine sinterable hydroxylapatite powder suitable for agglomeration may be prepared by any conventional granulating and/or particle sorting technique. Preferably, however, the fine particulate hydroxylapatite starting material employed herein is prepared by first preparing a gelatinous aqueous precipitate of hydroxylapatite, and then processing the precipitate into a sinterable fine dry powder suitable for use in the agglomeration process.

A suitable procedure for the preparation of an aqueous gel of hydroxylapatite is described by E. Hayek et al., Inorganic Synthesis, 7, 63 (1963) which is incorporated herein by reference. Hayek et al. disclose the precipitation of hydroxylapatite using phosphate solution, in accordance with the following reaction scheme:



The reaction disclosed by Hayek et al. leads to a gelatinous precipitate or hydroxylapatite which must be maintained in contact with the original solution or mother liquor until the molar ratio of calcium to phosphorus in the precipitate reaches the stoichiometric proportions characteristic of hydroxylapatite, i.e., about 5:3 or 1.67.

Once the stoichiometric proportions of calcium and phosphorus characteristic of hydroxylapatite are obtained, the gelatinous precipitate is separated from the mother liquor,

and the precipitate is washed to substantially reduce or, if desired, to eliminate the ammonium nitrate present in the gelatinous product. Since ammonium nitrate decomposes into gaseous by-products at temperatures of about 180°C to about 300°C, the generation of gas from ammonium nitrate during the heating of the agglomerate can lead to a breakup or weakening of the agglomerated hydroxylapatite precipitate by resuspending the precipitate in water, centrifuging the suspension, and then decanting the water.

The gelatinous precipitate of hydroxylapatite is next dried and converted into fine particles. The foregoing may be accomplished by way of a number of different drying or granulating techniques. Drying techniques which can be used include, for example, tray drying, vacuum drying, etc. If desired, the dried particles may be ground and then classified in order to obtain particles within the desired particle range.

Spray drying is the preferred technique for converting the gelatinous precipitate of hydroxylapatite into the fine dry particles suitable for use in the agglomeration process. The gelatinous precipitate may be spray dried by first preparing an aqueous slurry of the precipitate suitable for spray drying. The slurry may have a solids content of about 5% to about 15%, preferably about 7% to about 10% by weight, and the slurry may then be spray dried to provide particles within the desired size range.

Spray drying may be conducted at

temperatures of less than 400°C, e.g., in a conventional spray dryer employing an air inlet temperature of about 250°C, and an outlet temperature of about 115°C. Under these conditions the spray-dried hydroxylapatite particles are in a substantially anhydrous state, and the hydroxylapatite is no longer gelatinous, but may contain some chemically bound water. The spray-dried product obtained is in the form of dry porous particles of hydroxylapatite which cannot be reconstituted into the gelatinous state by the addition of water. Moreover, the spray-dried particles of hydroxylapatite are substantially spheroidal in shape.

The finally sintered hydroxylapatite agglomerates of this invention preferably have a porosity sufficient to permit the desired degree of tissue ingrowth to ensure proper attachment when the ceramic is employed for prosthetic purposes or as an implant material. The preferred hydroxylapatite ceramic produced in accordance with this invention is substantially spheroidal in shape and has a bulk particle density of about 80% to about 95% of the theoretical maximum density of pure hydroxylapatite. Moreover, the ceramic hydroxylapatite product includes an extensive network of micropores extending throughout the product, as seen by Scanning Electron Microscopic analysis. The individual pores which form the network are preferably all less than about 40 to about 50 microns (maximum pore diameter) in size. Most preferably, the median pore size is about 1.5 microns as determined by mercury porosimetry, with

about 90% of the pores being less than about 0.3 microns.

In further aspects of this invention, the finely sintered ceramic particles produced by the method of this invention may be combined with an orally compatible binder material and employed as a dental restorative material used to fill lesions caused by periodontal disease, or to augment or restore the alveolar ridge. The dental restorative compositions may also be employed as a tooth filling material, a dental liner, to mold or cast artificial teeth, etc. The spheroidal ceramic particles of this invention which employ pure hydroxylapatite are preferred for use in such dental restorative compositions because hydroxylapatite possesses a thermal coefficient of expansion substantially identical to that of natural tooth enamel, the hardness hydroxylapatite is similar to the hardness of natural tooth, and in addition natural tooth and hydroxylapatite stain in a similar way.

The preferred dental restorative compositions of this invention are comprised of about 5% up to about 90% by weight of the hydroxylapatite ceramic of this invention dispersed within about 10% to about 95% by weight of an orally compatible secondary binder.

Suitable binders for use in the preparation of the dental restorative materials of this invention, and particularly those employed to augment or restore the alveolar ridge, or to fill periodontal lesions, include secondary binders such as a binder comprised of plaster of paris

(calcium sulfate hemihydrate) and water. Alternative secondary binding materials include polymeric or polymerizable materials in combination with the appropriate additives for hardening the binder, e.g., crosslinking agents, polymerization catalysts, diluents, etc.

The polymeric or polymerizable secondary binder may be selected from a broad group of known polymeric materials suitable for use in the oral cavity. Such materials include, for example polymethacrylates such as hydroxylethylmethacrylate, polymethylmethacrylate, as well as other polyacrylic acids or esters, epoxy resins, polyesters, etc.

In addition, the ceramic particles produced in accordance with this invention may be admixed with a biocompatible inorganic or organic secondary binder, and then cast or molded into the form of a tooth, bone, a portion of a bone, etc. Bone prostheses prepared in this manner may then be surgically implanted employing conventional surgical techniques.

The spheroidal ceramic hydroxylapatite of this invention is also particularly well suited for use as a surgical implant material. For example, moist spheroidal particles of the hydroxylapatite ceramic in the size range of about 10 to 60 mesh may be used to fill properly prepared lesions caused by periodontal diseases. The moist hydroxylapatite is packed into the lesion following known periodontal procedures. In addition, the ceramic hydroxylapatite ceramic of this invention may be diluted with a biocompatible

diluent such as saline solutions or even blood, and injected into or about the alveolar ridge in order to augment or restore portions of that ridge, in accordance with known surgical procedures. For this purpose the spheroidal hydroxylapatite ceramic is preferably in about the 10 to about 60 mesh range.

When surgically filling or packing a periodontal lesion or another undesired void with the ceramic particles of this invention, it is desirable to completely fill the void. Advantageously, when a periodontal lesion or another void is packed with spheroidal ceramic of this invention, the ceramic filling substantially retains its original volume with little or no reduction in the volume of the filling material due to the settling of the particles in the void. In contrast, irregularly shaped non-spheroidal particles tend to settle in a void causing an undesired reduction in the volume of the filling material.

The crush strength, i.e., friability, of the ceramic particles produced in accordance with the present invention was measured by crushing 5 to 10 uniformly shaped particles (one at a time) of 20-40 mesh hydroxylapatite agglomerate in a Chatillon Model 1750B die shear tester. The average friability values presented in the following examples are given in pounds as read directly from the scale on the Chatillon tester.

This invention will be described further with reference to the following detailed Examples.

EXAMPLE 1

45.4 kg of calcium nitrate tetrahydrate was dissolved in 265 liters of deionized water and 62 kg of 26% ammonia water was added.

Separately, 15.2 kg of ammonium phosphate dibasic was dissolved in 378 liters of D.I. water and 28 kg of 26% ammonia was added. This solution was added into the solution of calcium nitrate under agitation which was then continued for 36 hours at ambient temperature. The slurry was then centrifuged through a split bowl centrifuge (Centrico, Inc. Model SB7). The solids were collected, dispersed in 500 liters of D.I. water and centrifuged again, dispersed once more in 500 liters of D.I. water and centrifuged. The collected solid is dried in a vacuum tray dryer at 80°C and 60 mm Hg pressure. Dry hard white lumps thus obtained were ground in a hammermill to pass an 80 mesh screen. Yield: 18.90 kg of $\text{Ca}_5(\text{OH})(\text{PO}_4)_3$ - 97.9%.

EXAMPLE 2

45.4 kg of the calcium nitrate was precipitated with ammonium phosphate exactly as described in Example 1. The precipitate was centrifuged and twice redispersed in 500 liters of D.I. water and centrifuged again. The gelatinous solid was dispersed in D.I. water again to produce a slurry with 8.3% of solids which was then spray dried using a Bowen spray dryer.

air inlet temperature: 250°C

air outlet temperature: 115°C

The product obtained was a white powder having a particle size of about 20-40 microns in the main fraction.

Yield: 17.60 kg of $\text{Ca}_5(\text{OH})(\text{PO}_4)_3$ - 91.1%

EXAMPLE 3

4.0 kg of hydroxylapatite powder prepared as described in Example 1 was charged into Glatt powder coater/granulator GPCT 5-9.

400 g of pregelatinized starch was dissolved in 4600 g of D.I. water.

The rotor was turned on and speed adjusted at 400 rpm, the air let temperature was 70°C and a starch solution was sprayed-in initially at 120 g/min., and later at 40 g/min. High initial flow rate is necessary to prevent loss of the dry fine powder. Agglomeration was monitored by sieving samples taken in approximately 5 min. intervals. Feeding of the starch solution was discontinued when the desired particle size was reached (approx. 60 min.); material was dried, discharged and sieved.

<u>Yield</u>	<u>Sieve Analysis</u>
4.45 kg -- 96.7%	+16 mesh 5.8%
	16-30 mesh 54.7%
	-30 mesh 39.5%

The fraction 16-30 mesh -- 2.43 kg -- was then charged into alumina crucibles and sintered; the material was heated to the temperature 1200°C at the rate of 8°C/min., temperature 1200°C was maintained 2 hours, material was cooled down to 300°C and removed from the furnace at this temperature. The product was weighed and sieved again.

<u>Yield</u>	<u>Sieve Analysis</u>
2.17 kg -- 89.3%	16-20 mesh 3.8%
	20-40 mesh 93.5%

-40 mesh 2.7%

EXAMPLE 4

5.0 kg of spray dried hydroxylapatite powder, prepared as described in Example 2, was charged into the Glatt GPCG 5-9 granulator.

400 g of pregelatinized starch was dissolved in 4600 c of D.I. water. The rotor was turned on at 400 rpm and starch solution sprayed in at 120 g/min initially, and later at a rate of 40-60 g/min. Feeding of the starch solution was discontinued when the desired particle size is reached. The material was then dried and discharged.

Yield

4.55 g -- 91.-%

Sieve Analysis

+16 mesh 6.7%

16-30 mesh 61.3%

-30 mesh 32.0%

The fraction 16-30 mesh -- 2.79 kg -- was sintered as described in Example 3.

Yield

2.63 kg -- 94.3%

Sieve Analysis

16-20 mesh 4.7%

20-40 mesh 91.5%

-40 mesh 3.8%

EXAMPLE 5

5.0 kg of spray dried hydroxylapatite powder, prepared as described in Example 2, was charged into a Glatt GPC 5-9 granulator.

1.00 kg of polyvinylpyrrolidone (PVP) K29-32 was dissolved in 4 liters of D.I. water. The rotor was turned on at 400 rpm and the binder solution was fed in at 120 g/min initially and later at 40-60 g/min. Feeding was discontinued when the desired particle size is reached. The

material was then dried and discharged.

<u>Yield</u>	<u>Sieve Analysis</u>
4.65 kg -- 93.0%	+16 mesh 16.3%
	16-30 mesh 73.5%
	-30 mesh 10.2%

The fraction 16-30 mesh -- 3.42 kg -- was sintered as described in Example 3.

<u>Yield</u>	<u>Sieve Analysis</u>
3.23 kg -- 94.4%	16-20 mesh 4.1%
	20-40 mesh 93.1%
	-40 mesh 2.8%

EXAMPLE 6

4.0 kg of the spray dried hydroxylapatite was preagglomerated to the particle size 40-60 mesh.

400 g of the pregelatinized starch was dissolved in 4600 g of D.I. water.

8.0 kg of the spray dried hydroxylapatite of particle size 20-40 microns was charged into the powder coating injection port.

The rotor was turned on at 400 rpm speed, starch solution was fed in at 80 g/min. and the powder injection was set for 8.0 kg/hr. Agglomeration of particles 40-60 mesh and coating of this preagglomerate took place simultaneously. The particle size 14-25 mesh was reached within 54 minutes. At this point the speed of the rotor was increased to 900 rpm feeding of the powder and the starch was discontinued, heating was stopped and material was sprayed with D.I. water for 10 minutes. Higher speed compacted the particles and increased their density and the particle size shrunk to the desired 16-30 mesh. The rotor speed

was brought down to 400 rpm, water spraying was discontinued and material was dried.

<u>Yield</u>	<u>Sieve Analysis</u>
11.34 kg -- 94.5%	+16 mesh 7.1%
	16-30 mesh 92.3%
	-30 mesh 0.6%

The fraction 16-30 mesh -- 10.47 kg -- was sintered as described in Example 3.

<u>Yield</u>	<u>Sieve Analysis</u>
9.69 kg -- 92.5%	16-20 mesh 5.7%
	20-40 mesh 92.9%
	-40 mesh 1.4%

EXAMPLE 7

5.1 kg of the off size, granulated hydroxylapatite of particle size +16 mesh and -30 mesh was ground in the hammermill to the particle size -80 mesh and charged into the Glatt GPCG 5-9 granulator. This material was a leftover from agglomeration as described in Example 4; and as such, it contained starch used in the agglomeration.

400 g of pregelatinized starch was dissolved in 4600g of water.

Rotor was turned on at 400 rpm speed and starch feeding started at 80 g/min. Agglomeration began within 10 minutes and the desired particle size 16-30 mesh was reached in 35 minutes. Faster response was due to the starch content in the starting material. The material was dried and discharged.

<u>Yield</u>	<u>Sieve Analysis</u>
4.90 kg -- 96.1%	+16 mesh 6.9%
	16-30 mesh 90.8%

-30 mesh 2.3%

The fraction 16-30 mesh -- 4.45 kg was sintered as described in Example 3.

Yield

4.13 kg -- 92.8%

Sieve Analysis

16-20 mesh 6.1%

20-40 mesh 90.9%

-40 mesh 3.0%

EXAMPLE 8

5.0 kg of the spray dried hydroxylapatite and 400 grams of pregelatinized starch were charged into the Glatt GPCG 5-9 granulator.

Rotor was turned on at 400 rpm speed and the fluidized powder was sprayed with D.I. water at the rate of 80 g/min. initially and at 40 g/min. rate later. Powder was gradually agglomerized and the spray of the water was discontinued when the main fraction reached the size 16-30 mesh. Material was dried and discharged.

Yield

5.2 kg -- 96.3%

Sieve Analysis

+16 mesh 5.7%

16-30 mesh 90.9%

-30 mesh 3.4%

The fraction 16-30 mesh -- 4.73 kg -- was sintered as described in Example 3.

Yield

4.38 kg -- 92.6%

Sieve Analysis

16-20 mesh 2.8%

20-40 mesh 93.7%

-40 mesh 3.5%

EXAMPLE 9

5.0 kg of the agglomerated hydroxylapatite of the particle size 20-30 mesh

was charged into the Glatt GPCG 5-9 granulator with a Wurster column insert.

Sludge of the hydroxylapatite was prepared as described in Example 2, redispersed in D.I. water and centrifuged again twice and diluted with D.I. water to contain 7% solids.

40 kg of this sludge was weighed; 300 g of pregelatinized starch was added and dissolved in the sludge and this mixture was then sprayed on the fluidized bed of granulated hydroxylapatite in the Wurster column at the flow rate 40-60 g/min. The product was dried, discharged and sieved.

<u>Yield</u>	<u>Sieve Analysis</u>
7.72 kg -- 91.0%	+16 mesh 4.1%
	16-30 mesh 95.4%
	-30 mesh 0.5%

The fraction 16-30 mesh -- 7.36 kg -- was sintered as described in Example 3.

<u>Yield</u>	<u>Sieve Analysis</u>
6.92 kg -- 94.04%	16-20 mesh 11.1%
	20-40 mesh 88.1%
	-80 mesh 0.8%

EXAMPLE 10

12-60 mesh hydroxylapatite was agglomerated with polyvinyl pyrrolidone (PVP) binder generally following the agglomeration procedures set forth in the preceding Examples.

The binder was extracted as follows: 20 g of the PVA agglomerated hydroxylapatite was added to a solution of 2 ml isopropyl alcohol and 100 ml D.I. water heated to a boil, allowed to cool for 2 hrs., decanted, dried at 110°C to substantially constant weight and fired at 1200°C

for 2 hours.

Yield
9.8 g

Friability
6.2

EXAMPLE 11

The procedure of Example 9 was repeated except that the binder extraction step was carried out in 2 mls ammonium hydroxide and 100 ml D.I. water.

Yield
10.6 g

Friability
6.0

EXAMPLE 12

Four different batches of hydroxylapatite agglomerated with polyvinylpyrrolidone (PVP) binder were prepared generally following the procedure of Example 5.

The PVP binder was extracted from a sample of each batch of PVP agglomerated hydroxylapatite as follows:

10g of the PVP agglomerated hydroxylapatite was added to 40 ml isopropyl alcohol (IPA), boiled, cooled for 2 hours, decanted, dried at 90°C to substantially constant weight and sintered at 1200°C for 2 hrs.

<u>BATCH NO.</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>
Yield (after ext'n & drying)	8.2gm	7.7gm	7.9gm	7.8gm
Yield (after sintering)	6.1gm	6.2gm	6.1gm	6.2gm
Friability	5.3	6.1	6.5	6.4

EXAMPLE 13

Binder was extracted from three batches of PVP agglomerated hydroxylapatite prepared generally in accordance with the procedure of

Example 10 as follows:

About 1 liter of isopropyl alcohol was charged in the extraction chamber of a Soxhlet-type extractor with about 1.5 kg of PVP agglomerated hydroxylapatite and refluxed for 48 hours. The extracted material was removed from the extractor and dried to constant weight. Samples periodically taken from the extractor showed, the following reduction in binder content:

<u>TIME (Hrs)</u>	<u>0</u>	<u>5</u>	<u>10</u>	<u>48</u>
% PVP (removed)	0	10	40	84

EXAMPLE 14

An extraction generally following the procedure of Example 11 was repeated and yielded the following result:

<u>TIME (Hrs)</u>	<u>0</u>	<u>2</u>	<u>24</u>	<u>49</u>	<u>73</u>
% PVP (present)	20	12	15	13	0.2

EXAMPLE 15

Batches of hydroxylapatite agglomerated with polyvinyl alcohol, polyvinylpyrrolidone, hydroxypropyl cellulose, and starch binders were prepared generally following the procedures set forth in the preceding Examples.

Samples from each batch of the hydroxylapatite agglomerates were placed in an oven having an oxygen atmosphere and heated at the rate of 20°C per min. to 500°C each producing white material which produced acceptable ceramics, i.e. Friability greater than about 3.0, and an unchanged X-ray diffraction pattern (approximately 100% hydroxylapatite).

What is claimed is:

1. A method for preparing sintered ceramic particles of a calcium phosphate compound comprising:

a) agglomerating together dry particles in the size range of 1-75 microns of a sinterable powder of said compound with a binding agent to provide sinterable agglomerates having a size range of about 10-80 mesh;

b) extracting an amount of binder from said agglomerates sufficient to provide sintered agglomerates which do not exhibit carbonized binder discoloration when said agglomerates are subjected to sintering temperatures; and

c) subsequently sintering said agglomerates to provide said ceramic particles.

2. The method according to Claim 1 wherein said extraction step comprises heating said agglomerates to a first temperature less than their sintering temperature to extract said binding agent.

3. The method according to Claim 2 wherein said heating to said first temperature is conducted in an oxygen enriched atmosphere.

4. The method according to Claim 3 wherein said heating to a first temperature is at the rate of about 20°C/minute and said first temperature is about 500°C.

5. The method according to Claim 1 wherein said extraction step comprises extracting said binder from said agglomerates with a liquid

and separating the agglomerate from the liquid before said sintering step.

6. The method according to Claim 5 wherein said binding agent is selected from the group consisting of starch, pre-gelatinized starch, polyvinyl alcohol, polyvinylpyrrolidone, and hydroxypropyl cellulose.

7. The method according to Claim 6 wherein said liquid is selected from the group consisting of methanol, isopropyl alcohol, methylene dichloride and aqueous solutions thereof.

8. The method according to Claim 1, wherein said sinterable particles are selected from the group consisting of tricalcium phosphate, hydroxylapatite, or mixtures thereof.

9. The method according to Claim 1 further comprising the step of preparing said sinterable particles by spray-drying an aqueous suspension of said sinterable particles to provide a fine dry powder comprised of said sinterable particles.

10. The method according to Claim 1, wherein said sinterable particles are comprised of hydroxylapatite and wherein said agglomerate is substantially spheroidal in shape.

11. The method according to Claim 1 wherein said agglomerate is prepared by applying said binding agent to a rotating fluidized bed of said sinterable particles.

12. The method according to Claim 1 wherein a major portion of said agglomerate is in about the 16 to 30 mesh range.

13. The method according to Claim 1 wherein an aqueous gel of hydroxylapatite is diluted with water and then spray-dried to provide a dry powder of porous sinterable hydroxylapatite particles, in the size range of about 1 to about 75 microns, said agglomerates are prepared by applying a binding agent to a rotating fluidized bed of said dry hydroxylapatite particles, to provide substantially spheroidal particulate agglomerates in the size range of about 10 to about 80 mesh; said agglomerates are heated to an elevated temperature below about 700°C to substantially eliminate said binding agent and to provide an agglomerate of adherent hydroxylapatite particles which is substantially free of residue of said binding agent, and said agglomerate is sintered at a temperature of about 1000°C to about 1300°C for about 1 to about 3 hours to provide ceramic hydroxylapatite particles which are substantially spheroidal in shape, and include a network of micropores extending throughout said ceramic particles.

14. Ceramic particles of hydroxylapatite characterized by: a bulk density between 80% and 95% of the theoretical maximum density of pure hydroxylapatite; a size range of between 10 and 80 mesh; a substantially spherical shape; and a network of pores in the individual particles having a maximum pore diameter of 50 microns, with about 90% of the pores having a diameter of about .3 microns or less.

AMENDED CLAIMS

[received by the International Bureau on 18 May 1987 (18.05.87);
original claims 1 and 14 amended; claims 2-13 unchanged (2 pages)]

What is claimed is:

1. A method for preparing sintered ceramic particles of a calcium phosphate compound suitable for use as a human implant material, the method comprising:

a) agglomerating together dry particles in the size range of 1-75 microns of a sinterable powder of said compound with a binding agent to provide sinterable agglomerates having a size range of about 10-80 mesh;

b) extracting an amount of binder from said agglomerates sufficient to provide sintered agglomerates which do not exhibit carbonized binder discoloration when said agglomerates are subjected to sintering temperatures; and

c) subsequently sintering said agglomerates to provide said ceramic particles.

2. The method according to Claim 1 wherein said extraction step comprises heating said agglomerates to a first temperature less than their sintering temperature to extract said binding agent.

3. The method according to Claim 2 wherein said heating to said first temperature is conducted in an oxygen enriched atmosphere.

4. The method according to Claim 3 wherein said heating to a first temperature is at the rate of about 20°C/minute and said first temperature is about 500°C.

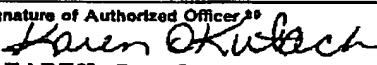
5. The method according to Claim 1 wherein said extraction step comprises extracting said binder from said agglomerates with a liquid

13. The method according to Claim 1 wherein an aqueous gel of hydroxylapatite is diluted with water and then spray-dried to provide a dry powder of porous sinterable hydroxylapatite particles, in the size range of about 1 to about 75 microns, said agglomerates are prepared by applying a binding agent to a rotating fluidized bed of said dry hydroxylapatite particles, to provide substantially spheroidal particulate agglomerates in the size range of about 10 to about 80 mesh; said agglomerates are heated to an elevated temperature below about 700°C to substantially eliminate said binding agent and to provide an agglomerate of adherent hydroxylapatite particles which is substantially free of residue of said binding agent, and said agglomerate is sintered at a temperature of about 1000°C to about 1300°C for about 1 to about 3 hours to provide ceramic hydroxylapatite particles which are substantially spheroidal in shape, and include a network of micropores extending throughout said ceramic particles.

14. Ceramic particles of hydroxylapatite characterized by: a bulk density between 80% and 95% of the theoretical maximum density of pure hydroxylapatite; a size range of between 10 and 80 mesh; a substantially spherical shape; and a network of micropores in the individual particles sufficient to permit tissue attachment when the particles are employed as an implant or prosthesis material, said micropores having a maximum pore diameter of about 50 microns, and a median pore diameter of about 1.5 microns.

INTERNATIONAL SEARCH REPORT

International Application No **PCT/US86/02830**

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ³ According to International Patent Classification (IPC) or to both National Classification and IPC IPC(4): B29B 9/08; B29C 67/04; C04B 33/32, 38/04 U.S. CL. 106/35; 264/12,43,63,65,66,117		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
U.S.	23/313FB; 106/1,35; 264/12,43,44,56,63,65,66,117	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category ⁶	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
Y	US,A, 2,463,550 (MYERSON ET AL) 08 MARCH 1949 See column 5.	1,5-8
Y	US,A, 2,593,507 (WAINER) 22 APRIL 1952 See column 2.	1,8-10
Y	US,A, 2,939,199 (STRIVENS) 07 JUNE 1960 See column 2.	1,5
A	US,A, 3,027,229 (TOWEY ET AL) 27 MARCH 1962	1,13
A	US,A, 3,043,652 (SCHYTIL) 10 JULY 1962	1,11
A	US,A, 3,322,867 (LEROY ET AL) 30 MAY 1967	1-4,13
A	US,A, 3,787,900 (MCGEE) 29 JANUARY 1974	1,8
Y	US,A, 3,881,911 (CHENEY ET AL) 06 MAY 1975 See columns 2 and 3.	1,9,13
A	US,A, 4,020,134 (GORDON ET AL) 26 APRIL 1977	1-6
Y	US,A, 4,097,935 (JARCHO) 04 JULY 1978 See abstract and column 7.	1,5,6,8,13
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁵ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ¹		Date of Mailing of this International Search Report ¹
20 FEBRUARY 1987		18 MAR 1987
International Searching Authority ¹		Signature of Authorized Officer ²⁰
ISA/US		 KAREN D. KUTACH

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No ¹⁸
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Y, P	US, A, 4,608,215 (GONCZY ET AL) 26 AUGUST 1986 See abstract.	1-4
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A, P	US, A, 4,629,464 (TAKATA ET AL) 16 DECEMBER 1986.	1,8
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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	US, A, 4,197,118 (WIECH, JR.) 08 APRIL 1980 See abstract and column 4 and 6.	1, 5-7
A	US, A, 4,218,255 (BAJPAI ET AL) 19 AUGUST 1980	1,8
A	US, A, 4,297,250 (GUPTA ET AL) 27 OCTOBER 1981	1
A	US, A, 4,340,555 (PROCTER) 20 JULY 1982	1
X	US, A, 4,551,436 (JOHNSON ET AL) 05 NOVEMBER 1985, See abstract and columns 2, 3, 4 and 9.	1-4, 12
Y,P	US, A, 4,563,315 (WALTER ET AL) 07 JANUARY 1986 See columns 3 and 6.	1, 11-13

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹⁰

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____, because they relate to subject matter ¹⁰ not required to be searched by this Authority, namely:

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹⁰, specifically:

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ¹¹

This International Searching Authority found multiple inventions in this international application as follows:

I. Claims 1-13 drawn to a method for preparing sintered ceramic particles; class 264, subclass 63.

II. Claim 14 drawn to ceramic particles; class 106, subclass 35.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

1-13

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.